Cardiovascular Physiology

Effects of Microgravity

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ABSTRACT: ***Experiments during spaceflight and its groundbase analog, bedrest, provide consistent data which demonstrate that numerous changes in cardiovascular function occur as part of the physiological adaptation process to the microgravity environment. These include elevated heart rate and venous compliance, lowered blood volume, central venous pressure and stroke volume, and attenuated autonomic reflex functions. Although most of these adaptations are not functionally apparent during microgravity exposure, they manifest themselves during the return to the gravitational challenge of earth's terrestrial environment as orthostatic hypotension and instability, a condition which could compromise safety, health and productivity. Development and application of effective and efficient countermeasures such as saline "loading," intermittent venous pooling, pharmacological treatments, and exercise have become primary emphases of the space life sciences research effort with only limited success. Successful development of countermeasures will require knowledge of the physiological mechanisms underlying cardiovascular adaptation to microgravity which can be obtained only through controlled, parallel groundbased research to complement carefully designed flight experiments. Continued research will provide benefits for both space and clinical application as well as enhance the basic understanding of cardiovascular homeostasis in humans.***

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More than 250 men and women have flown in space. With the more commonplace occurrence of observing people living and working in space, it has become attractive for some to assume that there are few significant medical problems associated with even long-term exposures to microgravity. Certainly the instability observed in early space travelers during immediate postflight ambulation has been well-documented. From the perspective of those medical personnel responsible for the care of astronauts, alterations in cardiovascular homeostasis that occur even after brief exposure to microgravity are of great significance. Important orthostatic hypotension and instability with standing are consistently reported in crewmembers,[1,2] and understanding and countering these concomitants of spaceflight have become a major focus of the Human Life Sciences Research Program in NASA.

Experimental investigation designed to understand alterations in the cardiovascular response to microgravity is limited by the fact that a comprehensive assessment of human physiology could not be accomplished in space. It has become clear that ground-based models designed to induce quantitative as well as qualitative physiologic changes would be very useful in providing laboratory control of experimental variables as well as relatively large sample size. Investigators noted that post-flight hemodynamic responses, referred to as "cardiovascular deconditioning," bore considerable similarity to those seen after prolonged bedrest. While not precisely analogous, bedrest does remove the head-to-foot gravitational gradient of the normal 1G environment and thus mimics, at least in part, the physiological adaptation to spaceflight. In addition, bedrest responses are of interest in and of themselves for their relevance to clinical issues of confinement. The difficulties inherent in rehabilitating otherwise

healthy patients who have been forced to remain in bed by orthopedic problems, for example, made it clear that bedrest-related changes in cardiovascular regulation merit clinical attention. The result of combining interests in cardiovascular alterations during spaceflight with clinical interests culminated in the completion of more than 160 studies since 1921 of the physiological responses to bedrest. Since astronauts universally describe a feeling of fullness in the head on the first day in space, head-down tilt has proven to better approximate this sensation and the resulting cardiovascular adaptations. Therefore, we will focus on the cardiovascular adaptation to microgravity and utilize data from both space experience and related ground-based bedrest studies.

CARDIOVASCULAR ADAPTATION TO MICROGRAVITY

Orthostatic hypotension and instability • One of the most immediately prominent effects of spaceflight is that cardiovascular function is compromised on return to earth, and this compromise is manifest in the upright posture by extreme hypotension and/or exaggerated tachycardia. Some degree of significant orthostatic instability has been described in about 30-40% of all crewmembers.[1,3,4]

In general, bedrest confinement has also induced a reduction in tolerance of the upright posture in healthy subjects.[5-8] The 40% incidence of syncope reported in one bedrest experiment[5] was remarkably similar to that reported in astronauts after spaceflight.[3] While the duration of bedrest has varied considerably, bedrest for one day can produce as much orthostatic tachycardia as two to three weeks of bedrest.[6] Clearly, if there were a more complete understanding of the detailed time course of cardiovascular adaptations induced by exposure to microgravity, physiologic mechanisms could be identified and appropriate countermeasures could be better designed. We will thus review the available data describing alterations in heart rate, arterial pressure, venous compliance, blood volume, cardiac function and neurohumoral factors, including baroreflex function, in an attempt to describe "cardiovascular adaptation" to microgravity and how these changes may contribute to orthostatic dysfunction upon return to terrestrial gravity.

Heart rate • In general, with only modest fluctuations, resting heart rate is unaltered during spaceflight.[9,10] Therefore, it seems most likely that elevated heart rate following spaceflight is an appropriate response to a reduced stroke volume in an attempt to maintain cardiac output and arterial pressure under the challenge of terrestrial gravity.

Slower resting heart rates have been reported in the first 24 hours of bedrest[5,11-13] followed by a gradual return to baseline levels over the first week.[11-12] Heart rate increases by 10-30 beats per minute between 10 and 120 days of bedrest[13] suggesting that microgravity gradually elevates resting heart rate.[5,14] The mechanism is unclear, but reduced vagal tone probably contributes as evidenced by lower R-R interval variability.

Arterial and venous pressures • During spaceflight, resting arterial blood pressure is altered very little.[10,15] The constancy of resting baseline arterial blood pressure in microgravity compared to terrestrial gravity indicates that changes in cardiovascular function associated with spaceflight represent appropriate homeostatic adaptations rather than dysfunctions.

Redistribution of body fluids toward the head and chest cavity during spaceflight led many investigators to the reasonable expectation that central venous pressure (CVP) would increase. Surprisingly, CVP decreased by nearly 60% during the seven-day D-1 Space Shuttle mission.[16] Although the use of a peripheral rather than central venous catheter raised some challenge to these findings, preliminary data from the recent SLS-1 mission confirms that following a transient elevation of CVP during the launch profile, venous pressure was lower immediately upon entering earth orbit in an astronaut instrumented with a central venous line. The reason for reduced CVP in microgravity is not clear, but may reflect an appropriate adaptation (resetting) of low-pressure baroreceptors in a low gravity environment where the redistribution of fluid to the upper body may not require as large a central pressure to maintain optimum cardiac filling as that needed in the upright posture on earth.

Like spaceflight, arterial pressure has generally remained unchanged for up to six months of bedrest.[1,5,8] While elevated blood pressure has occasionally been reported, it has generally been minor and transient. On the other hand, the reduction in central venous pressure estimated with a similar technique used on the D-1 astronauts[16] has been confirmed after seven days of bedrest. Changes in CVP induced by head-down tilt tend to have the same time course as those in vascular volume, with an initial transient elevation followed by a fall at or below normal baseline levels. Parallel changes in venous pressure and vascular volume may indicate that constancy of venous capacitance is defended in microgravity. The response of both arterial and venous blood pressures to bedrest is virtually identical to those reported in actual microgravity, supporting the argument that this analog provides a ground-based model to study cardiovascular adaptations to actual spaceflight.

Cardiac function • Adaptation of cardiac function has a relatively slow time course with little change during the first five months of spaceflight. In most cases, there is virtually no change in the heart rate

and cardiac output responses to a standard exercise protocol and the ability to perform vigorous work with the arms or legs is unimpaired.[9,15] In the most recent SLS-1 mission, resting cardiac output actually increased as a result of higher stroke volume while resting heart rate remained at preflight levels. Thus, during the initial four to five months of spaceflight, cardiac responses indicate no significant impairment of myocardial function. However, lower intracardiac volume during and after spaceflight has been frequently demonstrated,[1,17-19] with end-diastolic volume (EDV) being reduced as much as 50%[17] and persisting as long as 14 days after flight.[18] The importance of this was demonstrated after Skylab 4, when the postflight exercise stroke volume was reduced by 5-fold more with upright exercise compared to supine.[9] The cause of lower cardiac volume is unclear but could represent something as simple as reduced filling or as serious as myocardial atrophy.

With space missions longer than five months, cardiac output during physical exercise can fall as much as 15%, primarily due to a 30% decrease in stroke volume.[7,19] A significant elevation in heart rate during exercise could not compensate for the reduced stroke volume. One interpretation of these data is that the reduction in cardiac output represents a loss of cardiac function during longer duration spaceflight. However, evaluation of the Frank-Starling relationship during rest and higher ejection fraction during exercise suggests that cardiac function per se may not be adversely affected by spaceflight and that lower cardiac output simply reflects less myocardial filling due to hypovolemia.[7]

Bedrest studies have confirmed data acquired in space. End-diastolic volume actually increases during the first 24 hours of bedrest, but stroke volume returns to baseline in six hours.[6,12] A diuresis then follows and echocardiographic studies have shown a 6-12% fall in EDV over a period of several weeks.[8,20] Like spaceflight, reduced EDV is associated with lower SV and cardiac output during exercise, even in the face of dramatically elevated heart rate.[21] However, increased ejection fraction during this exercise[21] is consistent with spaceflight data in suggesting that the reduction in cardiac output reflects the effects of hypovolemia on cardiac filling without compromise of normal cardiac function.

Venous compliance • Increased venous compliance in the legs has been consistently reported to occur early in spaceflight.[9,19,22] This might be due to a number of factors, including a fluid shift of as much as 1-1.5 liters from the legs to the central thoracic circulation as well as a loss of muscle mass in the legs due to disuse in microgravity.[22]

Bedrest produces similar changes in lower extremity vascular compliance with an early large reduction postulated to be caused by the central shift of fluid with an additional later gradual decrease when the muscle compartment is reduced in mass by atrophy.[23,24] This latter aspect can be prevented by muscle activity while bedrest continues, suggesting that atrophy associated with inactivity can contribute to increased compliance. Since low orthostatic tolerance has been linked to high compliance of the lower extremities,[25] it is possible that increased venous pooling in the legs during standing following adaptation to microgravity could contribute to reduced venous return and orthostatic instability.

Blood volume • Intravascular volume is reduced during spaceflight.[9] A significant rapid fall in plasma volume occurs, with a more gradual reduction in red cell mass,[26-28] probably due to a fall in erythropoietin levels.[28] Reduction in total circulating blood volume is closely related to greater tachycardia during orthostatic challenges after spaceflight[2,4,9] suggesting that vascular volume can be an important contributing factor to post-spaceflight orthostatic hypotension and instability.

Similar to the time course observed in spaceflight, a large reduction in intravascular volume is seen during the initial 24 to 72 hours of bedrest, followed by a slower, gradual plateauing by 30 days of exposure.[1,5,8] Once a new equilibrium is reached, the magnitude of hypovolemia is rather consistent ranging from 14% to 17% over a range of seven to 30 days of bedrest.[5,7,11] These reductions in circulating blood volume have been accompanied by a transient fall in ADH, plasma renin activity, and aldosterone[29-31] and a release of atrial natriuretic peptide, perhaps due in part to stimulation of pulmonary, atrial and carotid mechanoreceptors.[8] Like spaceflight, reductions in plasma and blood volume during bedrest are related to orthostatic hypotension and instability during reambulation[5,8,32]

Neurohumoral function • During the initial two months of spaceflight, there appears to be little change in neurohumoral function as evidenced by in-flight plasma and urine levels of epinephrine, norepinephrine, and dopamine that were similar to preflight levels.[33] However, after 84 days of spaceflight in the third U.S. Skylab mission, catecholamine excretion was reduced.[31] Following return from microgravity to earth, catecholamine release is generally excessive compared to preflight levels.[33,34] Together these data may indicate that the sympathetic nervous system has a slower time course of adaptation and that as the duration of microgravity exposure is increased, less sympathetic stimulation and discharge become apparent.

During bedrest, resting plasma norepinephrine levels are reduced.[35,36] However, as the period of bedrest exposure exceeds one month, there is virtually no change in resting plasma norepinephrine compared to ambulatory baseline levels.[5,35] However, venoconstrictive responses following two weeks of

bedrest were largely unaltered by exogenous norepinephrine but were attenuated by administration of tyramine.[37] Since tyramine releases norepinephrine from nerve endings, these results suggested that neurohumoral adaptation to microgravity might inhibit the ability of adrenergic neurons to either release or synthesize norepinephrine while vascular responses remain intact. In addition, adrenoreceptors might also become hypersensitive since isoproterenol infusion caused a greater rise in plasma renin activity during bedrest compared to before bedrest.[14] Thus, the absence of change in circulating catecholamine levels may not reflect important autonomic adaptations to microgravity which could dramatically alter neurohumoral function that contributes to orthostatic integrity in the upright posture.

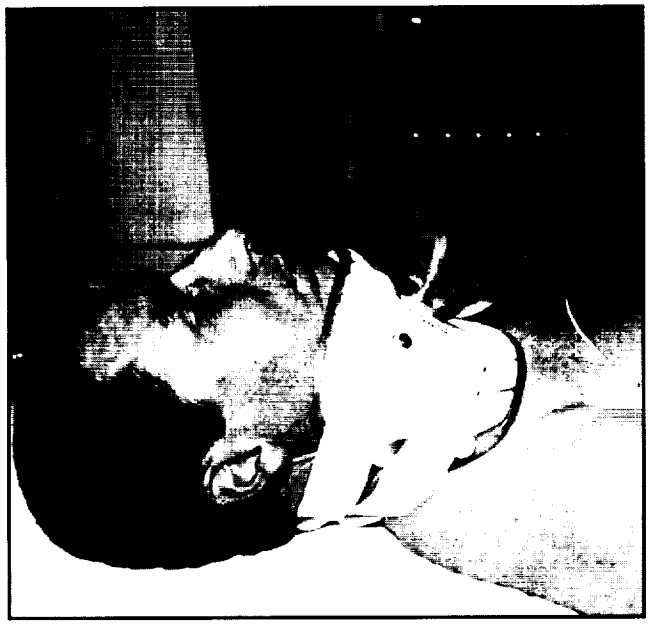

Fig. 1.—Carotid baroreceptor stimulation chamber (Barocuff).

Baroreflex function • As the duration of spaceflight lengthens, orthostatic instability persists despite efforts to restore body fluids with drinking,[38] suggesting that mechanisms other than vascular volume may be contributing to postflight orthostatic hypotension. The observation that standing heart rates begin to decline as the duration of spaceflight becomes longer than 10 to 12 days[39] raised the possibility that attenuation of cardioacceleratory baroreflexes may be part of the cardiovascular adaptation to longer duration spaceflight and can contribute to orthostatic hypotension by failing to maintain an appropriate cardiac output response to postflight standing. The development of a special neck chamber (Fig. 1) has allowed for noninvasive elaboration of the entire sigmoid baroreceptor-cardiac reflex response relationship in about 15 seconds during and after spaceflight. Using this technique, baroreceptor reflex dysfunction has subsequently been demonstrated during the SLS-1 flight and after spaceflight.[39] However, the logistical limitation to test orthostatic responses in astronauts immediately upon return to earth has made it difficult to determine any relationship between adaptation of baroreflex function and postflight blood pressure regulation.

Bedrest studies have corroborated the findings in spaceflight that baroreflex function is attenuated during and after exposure to microgravity.[5,40] Significant impairment of the vagally-mediated cardiac response to carotid baroreceptor stimulation was reported after 12 days of bedrest and significantly correlated with the magnitude of orthostatic hypotension during standing after bedrest.[5] The reduction of cardiac baroreflex sensitivity after bedrest was 6-fold greater in subjects who became syncopal upon reambulation compared to those who showed no syncopal symptoms. These fainters had less tachycardia in the

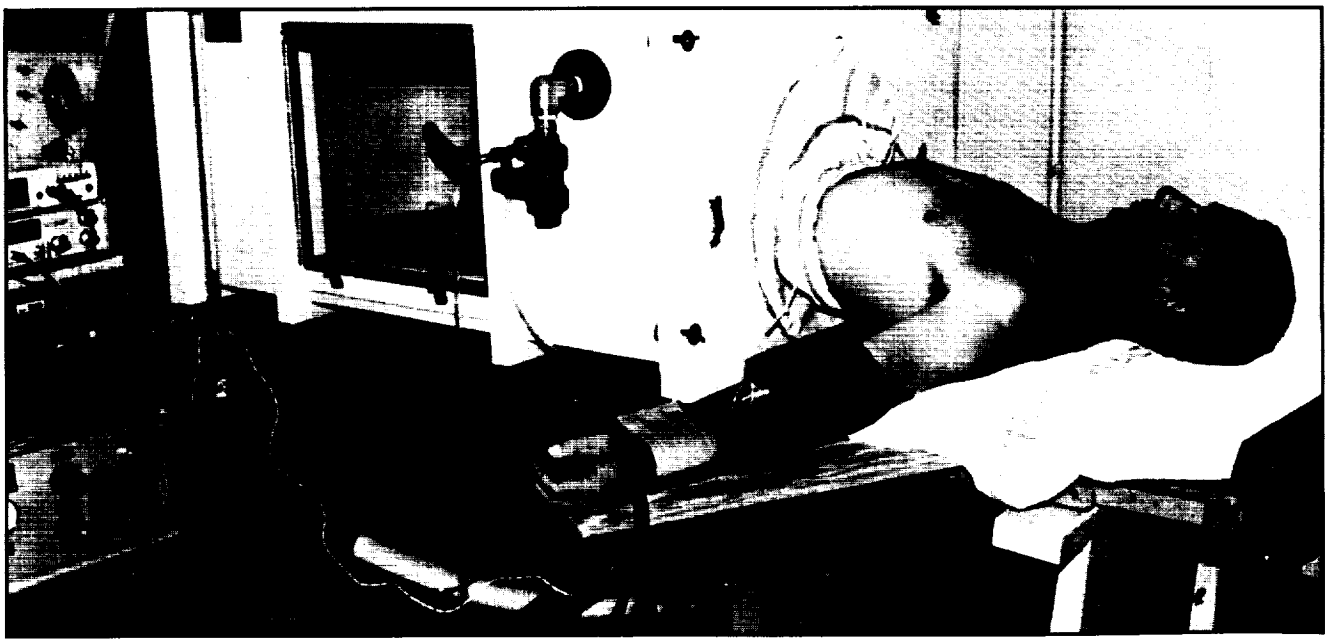

Fig. 2.—Lower body negative pressure (LBNP) device.

upright posture despite dramatically greater orthostatic hypotension. The magnitude of reduced tachycardia and its time course were similar to those reported in astronauts after spaceflight.[39] In addition to the cardiac response controlled by arterial baroreceptors, adaptation of atrial and pulmonary receptors or the reflex vasoconstrictor response they control may contribute to orthostatic hypotension with microgravity. Low levels of lower body negative pressure (LBNP less than 20 mmHg) is a technique that can be used to selectively isolate the response of this low-pressure baroreflex by systematically reducing CVP without altering arterial pressure[41] (Fig.2). Although this reflex has not been studied during or after spaceflight, recent bedrest experiments have demonstrated that microgravity causes a resetting of the cardiopulmonary baroreflex control of vascular resistance so that there is less peripheral vasoconstriction at the same central venous pressure. Clearly, attenuation of autonomic baroreflex functions asssociated with control of cardiac and vascular resistance responses is associated with the adaptation to microgravity but can compromise orthostatic stability upon return to the upright gravity environment.

DEVELOPMENT AND APPLICATION OF COUNTERMEASURES

Fluid replacement • One of the simplist and most common measures used to counter the effects of hypovolemia on postflight orthostatic instability has been the use of oral volume repletion with salt and water prior to landing. The prescription of salt and water provides approximately 1 liter of isotonic saline ingested about 2 hours prior to reentry. This procedure has proven partially effective in reducing orthostatic instability after spaceflights of short duration.[6,38] However, as missions approach one week or more in duration, "saline loading" becomes less effective so that the heart rate and blood pressure responses during a standard stand test postflight are no different in individuals who have taken the countermeasure from those who have not.[38] Unfortunately, the logistics of spaceflight make it difficult to accurately assess this countermeasure since compliance to the prescription cannot be controlled and direct measurements of blood volumes have not been obtained.

Surprisingly, the application of saline loading for astronauts in space developed with little rationale from ground-base experiments. In fact, the recent results of Vernikos and coworkers[42] demonstrated that the prescription of salt and water used by astronauts failed to restore plasma volume and prevent syncope in three of five subjects following seven days of headdown bedrest. These data are consistent with spaceflight results[38] and may explain the ineffectiveness of this treatment following missions of more than a week in duration. Certainly one would not expect volume loading alone to immediately correct all aspects of the orthostatic instability associated with adaptation to microgravity when other cardiovascular reflex control mechanisms may become impaired during this time course.

Intermittent venus pooling • The use of lower body negative pressure has been explored on the basis that intermittent venous pooling could be effective as a treatment for increased venous compliance and providing a stimulus for fluid retention. This procedure is currently part of the Soviet program applied during the five to seven days before reentry and, more recently, Space Shuttle crew members have begun its use. However, there are few supportive data at this time from these spaceflight experiences to draw conclusions about its effectiveness.

Intermittent venous pooling has been tested much more extensively during bedrest than in spaceflight. Plasma volume reduction has been minimized with a combination of LBNP at 30 mmHg for 4 hours/day and saline loading,[32] and with venous pooling alone using reversed gradient garments for 210 min/day.[43] However, there are a number of studies which demonstrate no benefit of these procedures with regard to improved orthostatic stability following bedrest.[8,44] Thus, the efficacy of this countermeasure for postflight orthostatic instability remains tenuous at best.

Pharmacological treatments • Pharmacologic therapy for cardiovascular control of blood pressure has not been employed during or after spaceflight but has been investigated in the bedrest setting. Using the concept that reduction of peripheral β-adrenoreceptor-mediated vasodilation could enhance elevation in peripheral resistance, β-blockade with propranolol was used to increase blood pressure stability at -70 mmHg of LBNP after bedrest. Overall, however, it decreased the total time that LBNP was tolerated despite a raised systemic vascular resistance,[45] suggesting that treatments for other factors that contribute to blood pressure regulation must be considered.

Ingestion of clonidine (0.45 mg/day) during bedrest has been investigated as a countermeasure against postbedrest orthostatic instability. Compared to control subjects, reduced changes in hematocrit, renin activity and aldosterone were reported in treated subjects suggesting that the drug was effective in ameliorating vascular volume changes. Venous compliance was reduced and orthostatic tolerance seemed to be improved.[46]

Fludrocortisone, a mineralocorticoid that aids in the retention of salt and water, has been examined as a possible countermeasure against postbedrest orthostatic intolerance with positive results.[47,48] In a recent recent study,[42] orthostatic stability during a 15-minute

stand test following seven days of bedrest was measured in six subjects who received fludrocortisone (0.2 mg every eight hours for 24 hours before ambulation) and compared with five subjects who received approximately 1 liter of isotonic saline following the prescription given to astronauts. Fludrocortisone restored plasma volume to prebedrest levels and five of six subjects completed the stand test with no noticeable difficulties. In contrast, standard "fluid loading" failed to restore plasma volume and three of the five subjects in this group became syncopal and could not complete 15 minutes of postbedrest standing. Clearly, these results are encouraging and provide a rationale for further testing of this technique in ground-based and spaceflight arenas.

Exercise • It is reasonable that exercise should become a candidate to be tested as a potential countermeasure since it can induce many cardiovascular adaptations that are opposite to those associated with postflight orthostatic intolerance. Exercise also has the potential to reduce musculoskeletal dysfunction. One to two hours of inflight exercise on a space treadmill in addition to use of spring-loaded "Penguin" or "Chibis" suits, which exerted a head-to-foot force and were worn eight hours/day, did prevent loss in aerobic capacity and muscle function, but postflight orthostatic hypotension persisted.[9] These results have led many to conclude that exercise may not be an effective countermeasure for postflight orthostatic instability.

Like spaceflight, exercise during bedrest has been effective in ameliorating the loss of aerobic capacity and muscle function as well as plasma volume[49,50] but has failed to enhance orthostatic stability following bedrest.[7] However, it is possible that exercise must be specific to provide that physiologic stimulus required to reverse the cardiovascular adaptations that contribute to postflight orthostatic hypotension. Exercise regimens that have been tested in space and during bedrest are conventional training programs of low to moderate intensity and long duration designed to challenge aerobic metabolism. In contrast, one bout of maximal exercise at the end of 10 days of bedrest restored aerobic capacity[50] and has acutely increased the sensitivity of the vagally-mediated cardiac baroreflex in ambulatory[51] and bedrested subjects.[40] It has been shown to increase plasma volume by 12%[52] and improve orthostatic tolerance after water immersion.[53] These effects would seem to differ from those of more chronically repeated exercise which, despite its ability to reduce leg muscle dysfunction and maintain plasma volume, does not seem to prevent postbedrest orthostatic instability.[7]

CURRENT AND FUTURE CONCERNS AND ISSUES

Because of the common perception that a reduction in physiological capacity with exposure to microgravity is a form of "deconditioning," it is relevant to consider whether changes in cardiovascular control that occur with spaceflight are truly dysfunctional or simply adaptive. It is clear that during spaceflight, astronauts function well after an initial period of adjustment. The cardiovascular system accustoms itself to the new microgravity environment and crewmembers are able to undertake physically strenuous tasks. Only during the gravitational challenge of reentry and on return to earth's terrestrial gravity environment do problems with cardiovascular homeostasis arise. Thus, one might well argue that humans adapt appropriately to two very different gravity environments, and that only the speed of adaptation is problematic.

The major issue has become clear that cardiovascular adaptation to microgravity can adversely affect orthostatic stability and performance of physical work immediately upon return to earth. With the early evolution of space travel, this did not impose a major problem since astronauts were "passive" passengers in space capsules. However, emergence of the Space Shuttle era requires astronauts to be orthostatically and physically functional to safely pilot a spacecraft back to earth much like a commercial aircraft as well as be prepared for the possibility of an emergency egress. This concern will take on greater proportions when future space activities include voyages of two to three years to travel to and inhabit Mars, requiring periodic entry into and out of various gravitational environments. The possibility that a pilot might be significantly less able to tolerate head-to-foot G forces during reentry and might lose functional consciousness at this critical time is of great concern and has sparked a serious interest in understanding and counteracting this problem. Because of its immediate impact on operational performance, effective clinical management of functional problems associated with cardiovascular adaptation to microgravity probably represents one of the most important concerns and challenges for future human spaceflight.

Development of effective and efficient countermeasures against postflight blood pressure dysfunction and orthostatic instability has, therefore, become a primary emphasis of the space life sciences research effort. Progress has been made in both understanding and beginning to treat the alterations in cardiovascular homeostasis associated with adaptation to microgravity, but many basic issues remain unresolved. Such issues as time required for application and amount of required resources must be considered for efficiency. It is unclear, for instance, whether countermeasures for cardiovascular changes should be applied near the end of a mission to allow appropriate adaptation to the microgravity environment to take place. More experiments are needed to better define the characteristics of fluid replacement

using saline loading treatments. If pharmacological treatments are to be developed and used, more information is required regarding possible side effects and other adverse reactions. Exercise regimens that require minimal use of oxygen, energy (food), and water must be carefully assessed. It must also be appreciated that the adaptation of the blood pressure control system is complex including alterations in many mechanisms that may require the combination of various countermeasure treatments. Most importantly, development of effective treatment requires the understanding of physiological mechanisms underlying cardiovascular adaptation to microgravity. As described previously, bedrest provides us with an appropriate ground-based analog for inducing cardiovascular adaptations to microgravity in a controlled laboratory setting, allowing for mechanistic experiments to be conducted. In the operational scenario of spaceflight, it is ethically difficult to employ placebo-controlled trials or to control compliance to required time and amount of treatments. It is also difficult to distinguish the early time course of adaptations and to obtain sample sizes large enough to allow meaningful conclusions. It is, therefore, paramount that we continue to develop a strong ground-based experimental program to parallel flight experiments in order to expedite the development of the most effective and efficient countermeasures.

Further investigation will be essential for maintaining and protecting optimal health, safety and productivity of space travelers, especially if long-duration manned flights are planned. As important, such continued research should reap significant benefits for the care of hospitalized patients confined to bed as well as enhance our basic understanding of cardiovascular control in humans.

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